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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/621,684	07/17/2003	Scott A. Waldman	TJU-2858	1770

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EXAMINER	
LIU, SUE XU	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 09/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/621,684	WALDMAN, SCOTT A.	
	Examiner	Art Unit	
	Sue Liu	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23,25-28,30-34,36 and 38-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,25-28,30-34,36 and 38-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/2/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Note the change of examiner for this application. (Please see the Conclusion paragraph for information on any future correspondence.)

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/2/06 has been entered.

Claim Status

Claims 1-22, 24, 29, 35, 37, have been cancelled as filed 8/2/06;

Claims 48-56 have been added as filed 8/2/06;

Claims 23, 25-28, 30-34, 36, and 38-56 are currently pending;

Claims 23, 25-28, 30-34, 36, and 38-56 are being examined in this application.

Election/Restrictions

1. Applicant's election without traverse of Group I (new claims 23-44), and species election of peptide having amino acid sequence of SEQ ID NO: 2 as the ST receptor

binding ligand, and 5-fluorouracil as the species of active agent, in the reply entered, 02/01/05, is previously acknowledged.

Applicants response to the restriction requirement addresses that the instant claim composition includes both conjugated and unconjugated compositions. Applicant's response has been considered and the instant claim pharmaceutical compositions are considered to include both conjugated and unconjugated compositions. No restriction between the conjugated or unconjugated compositions has been made, as previously acknowledged.

The newly added Claims 45-47 (as filed on 11/2/05) and Claims 48-56 (as filed on 8/2/06) are grouped together with the elected Group I, and are examined as one group of invention.

Priority

2. This application is a continuation of 09/263,477 (now abandoned), filed 3/5/99, which is a continuation of 08/583,447 (now US Patent 5,879,656), filed 1/5/96, which is a continuation-in-part of 08/141,892 (now US Patent 5,518,888), filed 10/26/93.

However, the Grandparent patent application 08/141,892 (Now US Patent 5,270,964) do not appear to provide supports for the claimed invention regarding SEQ ID NO: 55 and 56, which are recited in Claims 25, 32, 43, 45, and 50 of the instant application.

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent

application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Thus, the instant claims 25, 32, 43, 45, and 50 which recite sequences not disclosed in the parent applications are entitled only to the filing date of the application 08/583,447.

The filing date of the instant claimed invention of recited in Claims 25, 32, 43, 45, and 50 (in particular, SEQ ID Nos 55 and 56) is determined as the filing date of the US Application 08/583,447, **01/05/1996**.

Information Disclosure Statement

3. The references cited in the Information Disclosure Statement filed on 8/2/06 has been fully considered.

Specification

4. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

Claim Rejections Withdrawn

5. In light of applicants' amendments to the claims and supporting arguments, the following claim rejection as set forth in the previous Office action 2/2/06 is withdrawn:

A.) The written description rejection of claims 23, 28, 30-31, 41, and 42 under 35 U.S.C. 112, first paragraph, set forth in the previous Office action has been withdrawn. However, applicant's amendments and argument do not overcome the new rejections under 35 U.S.C. 112, first paragraph, as set forth below in the "New Rejections" section of the instant Office action.

Claim Rejections Maintained

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. The following Obviousness-type Double Patenting are maintained for the reason of record as set forth in the previous Office actions, 5/3/05 and 2/2/06:

A.) The rejection of claims 23-28, 41-42 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 5,962,220, set forth in the previous office action has been maintained for the reasons of record.

B.) The rejection of claims 23-28 and 41-42 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,060,037, set forth in the previous office action has been maintained for the reasons of record.

C.) The rejection of claims 23-28 and 41-42 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-19 of U.S. Patent No. 6,087,109, set forth in the previous office action has been maintained for the reasons of record.

D.) The provisional rejection of claims 23-25, 28-32, 35-36, 41-42 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 6, 8, 10, 32, 37, 9, 41-42, 54-55, 58, 63-64, 92, 96-97, 99, 102, 108, 109, 114, 116, 118-119, 125-153 of copending Application No. 08/468,449, set forth in the previous office action has been maintained for the reasons of record.

Discussion and Answer to Argument

7. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants traversed all the ODP rejections by arguing that no case of obviousness has been made in the previous Office Action (Reply entered 8/2/06 at p. 11, para 1 and p. 12, last para).

Contrary to applicant's assertion, the previous Office action mailed 5/3/05, at p. 11-12 has presented a prima facie case of how the instant claims are obvious over the cited reference patents and applications. However, the rejections are rewritten in addition

to new rejections that are necessitated by applicant's amendment to the claims in the "New Rejections" section of the instant Office action.

Applicants also specifically argue that the '037 patent claims are directed to methods of imaging colorectal tumors, in vitro methods of screening individuals, methods of treating colorectal tumors, methods of delivering nucleic acid molecules and kits. And the invention claimed in '037 patent corresponds to the non-elected groups in the present application, and the patent has no claims to conjugated compounds.

Applicants arguments and assertions regarding the '037 patent claims have been considered and are not persuasive. Because the original claims in the instant application 10/621,684 are drawn to pharmaceutical compositions, and methods of use of the compositions in *in vivo* methods. The independent claims in '037 patent are drawn to "method of radio imaging metastasized colorectal cancer cells by administering to an individual" (*in vivo* radio imaging, claim 1); and claim 3 is drawn to "*in vitro* method of screening an individual"; claim 5 is drawn to "*in vitro* method of determining whether tumor cell is a colorectal tumor cell'; and claim 10 recites a "kit for determining whether a sample contains a colorectal caner cell." And all claimed methods of the '037 patent use the same composition as that of the instant claims. In the instant application (10/621,684), only the methods of using the compositions comprising "ST receptor binding ligands" in *in vivo* methods were restricted from the compositions comprising "ST receptor binding ligands." The instant application does not have methods of use of ST receptor binding ligands *in vitro*. Thus, the obviousness-type double patenting rejection over the '037 patent is proper.

New Rejections

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description Rejection

9. Claims 23, 25-28, 30-34, 36, and 38-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims recite a product of pharmaceutical composition comprising: a) ST receptor binding ligand; b) a non-peptide radiostable therapeutic (or active) agent; and, c) a pharmaceutical carrier or diluent wherein said ST receptor binding ligand is selected from the group consisting of: a peptide, an antibody and fragments thereof.

To satisfy the written description requirement, applicants may convey reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.

Applicants may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. See, e.g., Vas-Cath, 935 F.2d at 1565, 19 USPQ2d at 1118.

The written description requirement of 35 U.SC. 112 exists independently of enablement requirement, and the requirement applies whether or not the case involves questions of priority. The requirement applies to all inventions, including chemical inventions, and because the fact that the patent is directed to method entailing use of compound, rather than to compound per se, does not remove patentee's obligation to provide a description of the compound sufficient to distinguish infringing methods from non-infringing methods. See Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 920-23, 69 USPQ 2d 1886, 1890-93 (Fed. Cir. 2004).

With regard to the description requirement, applicants' attention is invited to the decision of The Court of Appeals for the Federal Circuit, which held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it form other materials." University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1405 (1997), quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original) [The claims at issue in University of California v. Eli Lilly defined the invention by function of the claimed DNA (encoding insulin)].

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species or by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical an/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a

combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F. 3d at 1568, 43 USPQ2d at 1406.

Claims 23, 42, and 48 are drawn to a genus of "pharmaceutical compositions" comprising a genus of ST receptor binding ligand, and a genus of active (or therapeutic) agent. Neither the instant specification nor the claims have demonstrated common structure and/or function for the claimed genus of "pharmaceutical compositions" comprising various ST receptor ligands and active agents. In addition, no representative numbers of species for each claimed genus is provided to show possession of the claimed genus of "pharmaceutical composition" for using to treat various diseases. That is the claimed "pharmaceutical composition" can comprise any ST receptor binding ligand (i.e. any peptide, any antibody, and fragments thereof) and any active agent that can be any molecules.

The only examples of "pharmaceutical composition" are the conjugates used to inhibit T84 cells in vitro in the instant specification at p. 72-75 (especially Example 6). The instant specification does not disclose any pharmaceutical composition other than the conjugates used to inhibit the T84 cells. No example of "pharmaceutical composition" that can be used to treat human and/or animals for various diseases is described in either the instant specification or claims. That is the instant specification does not adequately describe compositions that can be used for pharmaceutical purposes including administering to humans and/or animals of the claimed peptide-agent conjugates.

In addition, the instant claims also drawn to a genus of peptides and/or antibody fragments, as discussed above. The term "fragments" is broad and encompasses

fragments comprises almost any numbers of amino acids. For example, a fragment can be a peptide comprising two amino acids, which when formulated to be a part of the pharmaceutical composition may or may not exhibit the desired pharmaceutical effects.

Therefore, applicants are not in possession of the claimed genus of "pharmaceutical composition" that comprises any ST receptor ligands and active agents. Applicant's claimed scope represents only an invitation to experiment regarding possible compositions that might be generated and used for pharmaceutical purposes.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

Scope of Enablement Rejection

10. Claims 23, 25-28, 30-34, 36, and 38-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for use in isolated cells, does not reasonably provide enablement for pharmaceutical uses in animals or humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. §112, first paragraph, have been described *In re Wands*, 8 USPQ2d 1400(1988). They are:

1. The breadth of the claims;
2. The nature of the invention;
3. The state of the prior art;
4. The predictability or lack thereof in the art
5. The level of skill in the art;
6. The amount of direction or guidance present;
7. The presence or absence of working examples;
8. The quantity of experimentation needed.

The breadth of the claims

The instant claims recite a product of pharmaceutical composition comprising: a) ST receptor binding ligand; b) a non-peptide radiostable therapeutic (or active) agent; and, c) a pharmaceutical carrier or diluent wherein said ST receptor binding ligand is selected from the group consisting of: a peptide, an antibody and fragments thereof.

The breadth of the claims seems to encompass pharmaceutical composition comprising ST receptor binding ligands that can be peptides or antibodies, and non-peptide therapeutic (or active) agent with intended therapeutic uses in animals or humans. However, the instant specification does not describe using the claimed peptides as parts of pharmaceutical compositions to treat diseases. The instant specification only prophetically discussed the possibility of using the claimed peptides in combination with therapeutic (or active) agents as pharmaceutical composition to treat various diseases such as cancer.

The nature of the invention

The nature of the invention as recited in the instant claims is pharmaceutical compositions with intended therapeutic uses to treat humans and/or other animals.

The state of the prior art/ The predictablility or lack thereof in the art

Utilization of peptides as pharmaceutical composition (especially administering to human) is highly unpredictable. There are many problems existing with the administering peptide drugs to human. First, the peptide drug may be toxic to the subject being administered, and hence will not elicit the intended pharmaceutical effects. To evaluate toxicity and efficacy of a peptide drug, pre-clinical animal model testing and clinical trials are required. Adverse effects of these peptide pharmaceuticals cannot be generalized, and are highly unpredictable. For example, Cianfrocca et al (British Journal of Cancer. (2006), pg 1-6) have reported a phase I clinical trial on a particular peptide drug with only limited success in treating patients with cancer.

Second, the mode of delivery for these peptide drugs is also critical, and the success of the delivery is highly unpredictable. The major problem with peptide pharmaceuticals is the mode of delivery. For example, Russell-Jones reviews oral delivery of peptide and/or protein drugs (Journal of Drug Targeting. Vol. 12(2): 113-123. 2004). The reference states that "peptide and protein pharmaceuticals, in contrast to the traditional chemically synthesized compounds, are highly susceptible to proteolysis within the intestine and also have very low oral bioavailabilities. The low oral bioavailability of these compounds is due to the almost impenetrable barrier provided by

the epithelial cell layer to certain types of molecules..." (see pg 113, left col.) The reference also teaches non-oral dosage forms are more difficult and traumatic to self-administer than oral dosages. Although methods of enhancing the delivery of peptide drugs into subjects are in development, "early attempts to enhance the oral uptake of many peptides and proteins were, in the main, unsuccessful" (see pg 121, left col., last para. of Russell-Jones reference).

Furthermore, the pharmaceutical conjugates claimed in the instant application may require delivery of the peptide drugs inside the cells to exert their pharmaceutical effects. This elicits additional problems such as specific cell targeting and cell penetration. El-Andaloussi et al (Current Pharmaceutical Design. Vol. 11: 3597-3611; 2005), throughout the reference, reviews cell-penetrating peptides. The reference teaches that the "major obstacle in the development of new therapeutic agents is the low bioavailability of hydrophilic substances. Drugs that bind to intracellular targets must penetrate the lipid bilayer surrounding the cell in order to exert their effect" (see Abstract of the reference). The reference also teaches that cell-penetrating peptides are of special structure and properties (pg 3598 of the reference). The instant specification does not shown that the claimed peptides can penetrate cells, or demonstrating their specific cell-penetrating structures and/or properties.

Therefore, the state of the art for using peptide pharmaceuticals to treat various diseases such as cancer or infectious disease is highly unpredictable. Although there are positive initial indications for the feasibility of using certain peptides for certain diseases in humans, there is no general demonstration of a successful treatment using peptides administered variously.

The level of one of ordinary skill

The level of skill would be high in order to carry out the intended use of the claimed pharmaceutical composition.

The amount of direction or guidance present / The presence or absence of working examples

The only examples of "pharmaceutical compositions" are the conjugates used to inhibit T84 cells in vitro in the instant specification at p. 72-75 (especially Example 6). The instant specification only recites that the tested cells (i.e. T84 cells) are incubated with the peptide-active agent conjugates, and then observing the inhibitory effect of the conjugates on the cells. There are no data indicating the peptide-conjugates' effects on any postulated diseases (such as cancer). No animal or human data are shown to indicate the pharmaceutical uses of the claimed peptides. That is no working examples are presented to demonstrate the pharmaceutical uses of the claimed peptides and their conjugates.

The quantity of experimentation needed

Due to the unpredictabilities of using peptides (and/or peptide conjugates) for treatment of various disease in any subject (as discussed supra), and the lack of guidance in the instant specification, undue experimentation would be required. Given the complications or mixed results of using peptides as pharmaceuticals to treat disease such as cancer, and the complexity in even developing a feasible peptide drug delivering

method, undue experimentation would be required. Because the art does not provide successful and general methods of administering peptides for treatment of various diseases, undue experimentation such as trial-and-error process would have to be employed for developing the various components for peptide pharmaceuticals including the mode of delivery, dosage requirement, toxicity testing, efficacy testing, etc.

Conclusion

Due to the non-routine experimentation necessary to determine the feasibility of using pharmaceutical composition comprising peptides for therapeutic uses; the lack of direction/guidance presented in the specification regarding the specific requirements for such a pharmaceutical composition; the unpredictability of the treatment methods using peptides as established by the state of the prior art; the breadth of the claims, undue experimentation would be required of a skilled artisan to make and/or use the claimed invention in its full scope.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 28, 30-34, 36, and 38-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 28, 30, 31, 32, 36, and 39 recite the limitation "said an active agent". There are insufficient antecedent bases for this limitation in the claims.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(Note: the instant claim numbers are in bold font.)

14. Claim 42 is rejected under 35 U.S.C. 103(a) as being unpatentable over Duflot et al (US 4,490,080; 2/12/1985; cited in the previous Office action 5/3/05), in view of Goers et al (US 4,867,973; 9/19/1989).

The instant claims recites a pharmaceutical composition comprising: a) a ST receptor binding ligand; b) a radiostable active agent; and, c) a pharmaceutical carrier or diluent wherein said pharmaceutical composition is a liposome comprising a vesicle matrix wherein the ST receptor binding ligand is in the vesicle matrix and the active agent is inside the liposome, and wherein said ST receptor binding ligand is selected from the group consisting of: a peptide, an antibody and fragments thereof.

Duflot et al, throughout the patent, teach pharmaceutical compositions comprising conjugates of ST receptor binding moiety (i.e., see claims 1-34) and an agent (toxin) (i.e., see claims 21-34), which reads on the pharmaceutical composition of **clm 42**. The 2nd peptide in Claim 18 or the cytotoxin of Claim 31 of the reference would read on the "radiostable active agent" of **clm 42** because the instant specification defines the term

"radiostable" as compounds which are not radioactive at p. 7, para 4. The reference also teaches buffers in which the said conjugates are contained for immunization (col. 15, lines 50+), and pharmaceutical compositions (e.g. Claim 33 of the reference), which reads on the pharmaceutical carrier or diluent of **clm 42**. The reference discloses ST receptor binding peptides comprising 18 amino acids of sequence Asn-Thr-Phe-Tyr-Cys-Cys-Glu-Leu-Cys-Cys-A-Pro-Ala-Cys-Ala-Gly-Cys-T, in which A and T each represent Tyr or Asn, and A and T are not the same (i.e., see Abstract or claim 1), which read on the SEQ ID Nos 2 and 3 of the instant claims.

Duflot et al do not specifically teach the pharmaceutical composition comprises a liposome.

However, Gluck et al, throughout the patent, teach a similar pharmaceutical composition comprising a liposome vesicle (part (a) of Claim 1 of the reference), a fusion peptide (part (b) of Claim 1), and a protein for binding receptor (part (d) of Claim 1). The reference teaches the benefits or advantages of using liposome vesicles to deliver particular drugs (col. 1, lines 55+). The advantages include facilitating transporting the drug through normally impermeable barriers, and improving drug selectivity and reduction in toxicity, etc. (col. 1, lines 57+).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to using liposome vesicles to deliver various drugs.

A person of ordinary skill in the art would have been motivated at the time of the invention to use liposome as part of a pharmaceutical composition that comprise fusion peptides (or conjugates) with active drug agents, because using liposome vesicle to

deliver drugs offer many advantages such as high permeability and low toxicity as discussed supra.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications because Gluck et al have demonstrated the utilization of liposome vesicle as part of a pharmaceutical composition that comprise peptides, and receptor binding proteins.

Double Patenting

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claims 23, 25-28, 33, 34, 38, and 40 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 5, and 6 of U.S. Patent No. 5,962,220 (cited in the previous Office action 5/3/05). Although the conflicting claims are not identical, they are not patentably distinct from each other because the reference patent claims the same pharmaceutical compositions as the instant application.

The '220 patent claims a pharmaceutical composition comprising a pharmaceutical carrier or diluent, and a conjugate compound comprising a ST receptor binding moiety and an active moiety (Claims 5 and 1 of the '220 patent), which reads on the receptor binding ligands of **clm 23**. The '220 patent also claims "active moiety" is an antisense molecule (claim 3), which reads on the non-peptide active (or therapeutic) agent of the instant claims (e.g. **clm 23**). The '220 patent also claims specific SEQ ID Nos 2, 3, and 5-54, which are the same as the SEQ ID Nos in the instant **clms 25-28, 33, 34, 38, and 40**.

17. Claims 23 and 28 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 6, and 8 of U.S. Patent No. 6,060,037 (Claims 5 and 1 of the '220 patent). Although the conflicting claims are not identical, they are not patentably distinct from each other because the reference patent claims the same pharmaceutical compositions as the instant application.

The '037 patent claims methods using a pharmaceutical composition comprising peptides as ST receptor binding moiety, the reference active moiety is a therapeutic

agent, and pharmaceutical acceptable carrier or diluent (e.g. Claim 8), which reads on the pharmaceutical composition of the instant **clms 23 and 28**.

18. Claims 23, 25-28, 33, 34, 38, and 40 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 7-10 and 13 of U.S. Patent No. 6,087,109 (Claims 5 and 1 of the '220 patent). Although the conflicting claims are not identical, they are not patentably distinct from each other because the reference patent claims the same pharmaceutical compositions as the instant application.

The '109 patent claims a pharmaceutical composition comprising a pharmaceutical carrier or diluent, and a conjugate compound comprising a ST receptor binding moiety and an active moiety (Claims 7 and 1 of the '109 patent), which reads on the receptor binding ligands of **clm 23**. The '109 patent also claims "active moiety" is an antisense molecule (claim 3), which reads on the non-peptide active (or therapeutic) agent of the instant claims (e.g. **clm 23**). The '109 patent also claims specific SEQ ID Nos 2, 3, and 5-54, which are the same as the SEQ ID Nos in the instant **clms 25-28, 33, 34, 38, and 40**.

19. Claims 23 and 28 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24, 26, 28, 29 and 33-41 of U.S. Patent No. 7,097,839. Although the conflicting claims are not identical, they are not patentably distinct from each other because the reference patent claims the same pharmaceutical compositions as the instant application.

The '839 patent claims methods using a pharmaceutical composition comprising peptides as ST receptor binding moiety, the reference active moiety is a therapeutic agent, and pharmaceutical acceptable carrier or diluent (e.g. Claims 11 and 20), which reads on the pharmaceutical composition of the instant **clms 23 and 28**. The '839 patent also claims the active agents are methotrexate, doxorubicin, 5-fluorouracil, etc. (e.g. Claim 22), which reads on the same active agents as the instant **clms 30, 31, 36, and 39.** The '839 patent also claims the pharmaceutical composition is in an injectable formulation (e.g. Claim 6), which reads on the injectable formulation of **clm 41**.

20. Claims 23, 25-28, 33, 34, 38, 40, 41, 42, 45, and 47 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 5, 6, 10, and 12 of U.S. Patent No. 5,962,220 in view of Goers et al (US 4,867,973; 9/19/1989).

The '220 patent claims a pharmaceutical composition comprising a pharmaceutical carrier or diluent, and a conjugate compound comprising a ST receptor binding moiety and an active moiety (Claims 5 and 1 of the '220 patent), which reads on the receptor binding ligands of **clm 23, and 42**. The '220 patent also claims "active moiety" is an antisense molecule (claim 3), which reads on the non-peptide active (or therapeutic) agent of the instant claims (e.g. **clm 23, 42 and 47**). The '220 patent also claims specific SEQ ID Nos 2, 3, and 5-54, which are the same as the SEQ ID Nos in the instant **clms 25-28, 33, 34, 38, 40, 45**. The '220 patent also claims the pharmaceutical composition is administered intravenously (e.g. Claim 12), which reads on the injectable formulation of **clm 41**.

The '220 patent does not specifically claims the pharmaceutical composition comprises a liposome.

However, Gluck et al, throughout the patent, teach a similar pharmaceutical composition comprising a liposome vesicle (part (a) of Claim 1 of the reference), a fusion peptide (part (b) of Claim 1), and a protein for binding receptor (part (d) of Claim 1). The reference teaches the benefits or advantages of using liposome vesicles to deliver particular drugs (col. 1, lines 55+). The advantages include facilitating transporting the drug through normally impermeable barriers, and improving drug selectivity and reduction in toxicity, etc. (col. 1, lines 57+).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to using liposome vesicles to deliver various drugs.

A person of ordinary skill in the art would have been motivated at the time of the invention to use liposome as part of a pharmaceutical composition that comprise fusion peptides (or conjugates) with active drug agents, because using liposome vesicle to deliver drugs offer many advantages such as high permeability and low toxicity as discussed supra.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications because Gluck et al have demonstrated the utilization of liposome vesicle as part of a pharmaceutical composition that comprise peptides, and receptor binding proteins.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached at 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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